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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,017	08/04/2008	Jacob Bar-Tana	1567/76581/JPW/CH	7859

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,017	BAR-TANA ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-19 and 23-31* is/are pending in the application.

4a) Of the above claim(s) *2-10 and 12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on January 6, 2011.

Receipt of Declarations under 37 CFR 1.132 is acknowledged.

Status of Claims

Cancellation of claims 1 and 20-21, amendment of claims 11 and 22-29, and addition of claims 30-31 is acknowledged.

Claims 2-19 and 23-31 are currently pending and are the subject of this office action.

Claims 2-10 and 12-19 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claims. Election was made **without** traverse in the reply filed on April 26, 2010.

Claims 11 and 22-31 are presently under examination.

The following species is under examination: Dyslipoproteinemia as the disease being treated.

Priority

The present application is a 371 of PCT/IL04/001185 filed on 12/30/2004, and claims priority to provisional application No. 60/533,639 filed on 12/30/2003.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (Maintained Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 22-29 and mew claims 30-31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bar-Tana 1 (US 6,303,653, cited in prior office action) and Bar-Tana 2 (US 6,284,903, cited in prior office action).

For claims 11 and 22-24 and 30-31 Bar-Tana 1 teaches a method of treating Syndrome X comprising administering a therapeutically effective amount of an amphipathic carboxylate. In a preferred embodiment each of the diseases comprising syndrome X may be treated individually (see column 4, lines 8-13, see also claim 8). The authors further define Syndrome X, also known as metabolic syndrome, as a combination of the following symptoms: dyslipoproteinemia, obesity, IGT/NIDDM, hypertension and coagulation/fibrinolysis defects (see column 2, lines 51-54). Among the amphipathic carboxylates the authors cite the compound: 3, 3, 14,14 tetramethyl

hexadecane 1, 16 dioic acid (MEDICA 16 or M16, see column 4, lines 60-61 and column 5, line 52) as one of the most active ones.

Bar-Tana 1 does not teach the dose ranges from about 30 mg per day to about 400 mg per day as disclosed in claim 11 or the dose range recited in claims 22-24 and 30-31. However, Bar-Tana 2 teaches that 3, 3, 14,14 tetramethyl hexadecane 1, 16 dioic acid (M16) is effective in reducing total cholesterol and plasma triglycerides (see Tables II and III) which offers an adequate treatment mode for combined hypertriglyceridemia-hypercholesterolemia (which comprise more than 70% of dyslipoproteinemic patients) (see column 2, lines 1-3). Further Bar-Tana 2 teaches a daily dosage of 50 to 5000 mg, which will depend on the age, needs and tolerance of the individual patient (see column 4, lines 61-67).

The dosage taught by Bar-Tana 2 (50 to 5,000 mg daily, see above) clearly overlaps with the dosages of the instant claims (30 to 400 mg daily, 100 to 400 mg daily, 200 to 400 mg daily, 100 to 200 mg daily, and 200 mg). MPEP 2144.05 states: In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Thus resulting in the practice of claims 11, 22-24 and 30-31 with a reasonable expectation of success.

For claims 25-29, Bar-Tana 2 further teaches that the daily dosage of the compound of formula (I) will depend on the age, needs and tolerance of the individual patient (see column 4, lines 64-67).

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to further optimize the dose regimen based on age, tolerance and the individual needs of the patient as taught by Bar-Tana 2, thus resulting in the practice of claims 25-29 with a reasonable expectation of success.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

Response to 37 CFR 1.132 declaration.

The declaration under 37 CFR 1.132 filed on January 6, 2011 is insufficient to overcome the rejection of claims 11 and 22-31 based upon 35 U.S.C. 103 (a) as set forth in the last Office Action.

For a full response to the arguments presented by Dr. Jacob Bar-Tana, please see discussion below.

Applicant argues that:

In response, for the purpose of expediting prosecution and without conceding the correctness of the Examiner's position, applicants have herein cancelled claims 1 and

20-21, and amended claim II which concerns the treatment of dyslipoproteinemia to recite "a range from about 30 mg per day to about 400 mg per day."

The claimed dosage range produces an unexpected result relative to the treatment of dyslipoproteinemia.

Applicants attach hereto, as Exhibit 1, a Declaration of Dr. Jacob Bar-Tana, M.D., Ph.D., and inventor named on the subject application which provides evidence that applicants' now claimed range provides an unexpected benefit when used to treat dyslipoproteinemia. See, Exhibit 1, page 3. In contrast, the maximum effect of M16 administration relative to insulin resistance, where the measured effect is insulin sensitization, occurs at higher dosages than those recited in amended claim 11, namely 400 to 600 mg/day. See, Exhibit I, page 5. The claimed benefit of M16 administration for treating dyslipoproteinemia could not have been predicted, and therefore would not have been obvious, from the disclosure of Bar-Tana 1 in view of the disclosure of Bar-Tana 2.

Examiner's response:

The experimental data provided by Applicant on Table 1 (see page 4 of the declaration and pages 2-3 for experimental protocol) is incomplete and does not prove any unexpected results for the treatment of dyslipoproteinemia in the range claimed by Applicant: 30 to 400 mg/day of M16.

Applicant claims that (see 132 declaration, page 3, third paragraph):

Table 1 presents the efficacy of M16 in lowering the plasma triglycerides and cholesterol levels of the Ml6-treated subjects. The data in Table 1 summarized in the

right column for all patients and the respective doses, indicate that M16 at doses of 30-200 mg/day decreased triglycerides by 42- 53% from base line. Dose escalation to 400 mg/day provided essentially the same decrease and did not produce any further significant decrease in TG, implying that the maximal efficacy for the TG lowering effect of M16 was reached using the 200 mg/day dose (see page 3, third paragraph).

However, the above experimental data has several flaws:

1- no single patient was treated with every dose range (30, 100, 200, 400, 500 and 600) of M16. For example for patients 105 and 106 the only data available is for the administration or 30, 100 and 200 mg/day of M16. As, expected, and for each individual (105 or 106) an increase in dose from 30 to 100 to 200 translated in a higher percent decline of TG.

2- The mean data on the right column is misleading since Applicant is comparing different groups of patients for each different dosage. For example at 30 and 100 mg/day Applicant is averaging the results of two patients: 105 and 106. However, at 200 mg/day, Applicant is averaging the result of 6 patients (101, 102, 103, 104, 105 and 106); at 400 mg/day, Applicant is averaging the result of 4 patients (101, 102, 103 and 104); at 500 mg/day, Applicant is providing the data of one patient: 102. And finally, at 600 mg/day, Applicant is averaging the data of two patients (102 and 103). This way the average data presented by Applicant is completely distorted because for example: the average at 200 mg/day (42.4) is lower than at 100 mg/day (53.2) which might seem that the efficacy of M16 will be lower at 200 mg/day than at 100 mg/day. However, this is the result of incorporating 4 new patients (101, 102, 103 and104) at the 200 mg/day

dose. There is no data available for those 4 patients at the 30 and 100 mg/day dosages, and as such it is not known what the average would have been for those two dosages if the data of these 4 patients would have been considered together with patients 105 and 106. In fact, when one considers the data for patients 105 and 106 only, at the 200 mg/day dosage the average would have been: 62.5 ((53.6 + 71.4) / 2) which, as expected, is much higher than the mean values at 30 (48.5) and 100 (53.2) mg/day for the same two patients.

In fact, when each patient is considered individually, any increase in dose amount translates in an increase in TG percentage decline as the dosage increases, with the only exception of patient 101 at 200 and 400 mg/day. For example, if one considers patient 103, the data will show that the percentage decline of TG at 200 mg/day is 54.4, at 400 mg/day is 57.6 and at 600 mg/day is 59.1. Also patient 102 shows the same trend: 6.4 at 200 mg/day, 6.9 at 400 mg/day and 8.1 at 600 mg/day.

The same argument holds true when one compares the mean values for the same group of patients. For example, the mean value for patients 101, 102, 103 and 104 for the 200 mg/day dose is: 32.37, and at 400 mg/day is 34.5. Again, an increase in percentage decrease in TG with an increase in the M16 dose is observed as expected.

3- Patient 102 seems to be an outlier. The decrease in TG is much lower than the other patients and in a much larger study it could probably have been eliminated. As such the so called mean result at 500 mg is completely distorted.

In summary, in order for the mean values to be meaningful, one has to compare the same group of patients throughout the different dosages. By incorporating and/or removing patients (particularly in such a small set) at different dosages, the mean values are not scientifically sound, since, as mentioned before, when each patient is taken individually, the data clearly shows that, as expected, an increase in the dosage of M16 causes an increase in the decline parentage of TG, including at 600 mg/day which is the highest dose tested by Applicant.

So Applicant has not provided any evidence that there something unexpected occurring with the dosage between 30 and 400 mg. To the contrary, as discussed above, it seems that the higher the dosage of M16 the higher the effect including at dosages above 400 mg/day.

Even if Applicant was able to demonstrate that there is no significant increase in efficacy after 400 mg/day, this could have not been considered an "unexpected" result, since it is known, with very few exceptions, that all active agents increase their efficacy with an increase in dose until they reach a maximum efficacy, above of which any dose increase causes no further increase in efficacy.

The data presented by Applicant in Exhibit 1, pages 5-6 regarding efficacy in insulin sensitization, is irrelevant, since Applicant is claiming the treatment of dyslipoproteinemia and not on insulin sensitization. In this regard, Applicant is referred to MPEP 716.01(b):

"*The weight attached to evidence of secondary considerations by the examiner will depend upon its relevance to the issue of obviousness and the amount and nature*

of the evidence. Note the great reliance apparently placed on this type of evidence by the Supreme Court in upholding the patent in United States v. Adams, 383 U.S. 39,148 USPQ 479 (1966).

To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir.), cert. denied, 488 U.S. 956 (1988)."

Applicant argues that:

Further, Tables II and III of Bar-Tana 2 disclose plasma triglyceride, plasma cholesterol, plasma apolipoprotein C-III, plasma glucose, and plasma insulin levels observed in rats fed a diet containing 0.09% (w/w) of one of the following compounds: (I) γ-γ'-methyl hexadecane α,ω-dioic acid, (2) α-α'-methyl hexadecane α,ω -dioic acid, or (3) β-β'-methyl hexadecane α,ω -dioic acid (MI6). See, Bar-Tana 2, column 5, line 35 to column 6, line 20. Importantly, Bar-Tana 2 does not disclose any data which shows

the effects of varying doses of these compounds on plasma triglyceride, plasma cholesterol, plasma apolipoprotein C-III, plasma glucose, and plasma insulin levels in human. Bar-Tana 1 is similarly silent. Thus, one of ordinary skill in the art at the time of applicants' invention could not have predicted that the maximum effect of MI6 administration in terms of treating dyslipoproteinemia would occur at a dosage between about 30 and about 400 mg per day.

Examiner's response:

Bar-Tana 2 clearly teaches a human dosage of 50 mg to 5000 mg/day depending, among other factors, on age, needs and tolerance of the individual patient (see column 4, lines 61-67). These recommended dosages overlap with the instant ones (see 103 rejection above) as such it will be obvious to select a dose range overlapping with 50 to 5000 mg/day and expect the treatment to still be effective. MPEP 2144.05 states: In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Applicant argues that:

Further, one of ordinary skill in the art could not have predicted that the maximum effect of M16 administration in terms of treating insulin resistance would occur at a dosage between about 400 and about 600 mg per day.

Examiner's response:

Regarding the data presented by Applicant in Exhibit 1, pages 5-6 regarding efficacy in insulin sensitization, is irrelevant, since Applicant is claiming the treatment of dyslipoproteinemia and not on insulin sensitization. In this regard, Applicant is referred to MPEP 716.01(b):

"*The weight attached to evidence of secondary considerations by the examiner will depend upon its relevance to the issue of obviousness and the amount and nature of the evidence. Note the great reliance apparently placed on this type of evidence by the Supreme Court in upholding the patent in United States v. Adams, 383 U.S. 39,148 USPQ 479 (1966).*

To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir.), cert. denied, 488 U.S. 956 (1988)."

Applicant argues that:

The Phase IIa human clinical study data disclosed in Exhibit 1 demonstrates that the dose range of M16 which is maximally effective to treat dyslipoproteinemia is different than the dose range of M16 which is maximally effective to treat insulin resistance. As explained above, this result would net have been obvious to one of ordinary skill in the art at the time of applicants' invention from any combination of the disclosures of Bar-Tana 1 and Bar-Tana 2. See also, Exhibit 1, page 6.

Examiner's response:

First, and as discussed above, the data presented by Applicant in Table 1 of the declaration is not evidence of any unexpected result, and there is no conclusive data on which dose range M16 is effective.

Second, and also as discussed above, the data regarding insulin resistance is irrelevant since it is not related to what is claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/

Examiner, Art Unit 1628
February 8, 2011.